ORAL FOOD CHALLENGE FAILURES AMONG FOODS RESTRICTED DUE TO ATOPIC DERMATITIS

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Abstract

BACKGROUND: Recent studies have suggested that removing foods from the diet to manage atopic dermatitis (AD), based on positive allergy tests, may lead to immediate allergic reactions on reintroduction of that food.

OBJECTIVE: The purpose of this study was to examine the frequency of oral food challenge (OFC) failures among foods removed from the diet as suspected AD triggers, focusing on the five major food allergens in the US.

METHODS: OFCs to egg, milk, peanut, soy, and wheat, performed from 2008-14, at a children's hospital's allergy clinics, were reviewed. OFCs were offered based on history and laboratory values. Reasons for food avoidance were classified as food allergy (IgE-mediated reaction occurring within two hours); sensitization only (lack of introduction due to positive test results); and removal due to test results during AD evaluation.

RESULTS: There were 442 OFCs performed, with 89 failures (20.1%). Reasons for OFCs included a history of food allergy (320/442; 72.4%); food sensitization without any introduction (77/442; 17.4%); and AD (45/442; 10.2%). OFC failures among those who had food allergy (70/320; 21.9%); sensitization only (13/77; 16.9%); and suspected AD trigger (6/45; 13.3%) did not significantly differ (p=0.63). Wheat was more likely to be avoided than the other four foods for AD concerns (p<0.0001).

CONCLUSION: The frequency of OFC failure among those who removed foods suspected as AD triggers was 13.3%, indicating a loss of tolerance. Restriction of foods to manage AD must be done with caution and close monitoring.

Keywords

Oral Food Challenges; Food Allergy; Atopic Dermatitis; Loss of Oral Tolerance

Abbreviations: Oral Food Challenges, (OFCs); Atopic Dermatitis, (AD); Skin prick test, (SPT); specific IgE, (sIgE)

INTRODUCTION

Common reasons for food avoidance include a history of IgE-mediated allergic reactions to a food; positive skin prick tests (SPTs) and/or specific IgE (sIgE) results to a food, without any exposure to the food (sensitization without introduction); and removal of a food from the diet due to positive SPT and/or sIgE results found during an evaluation for atopic dermatitis (AD). (1,2,3,4)

AD affects 10-30% of children in industrialized countries.(4) Up to 40 percent of children with moderate to severe AD have been reported to have an IgE-mediated food allergy.(1) Food-triggered AD is defined as having a positive SPT and/or sIgE to a food, in addition to a clinical history of worsened AD upon introduction of the food, and improved AD on removal of the food. (5,6) Patients with AD have rates of sensitization to foods ranging from 30 to 80 percent. (7,8,9) Accordingly, both SPT and sIgE can have low positive predictive values in determining culprit foods as AD triggers. (7,10)

Evaluating the role of food sensitization in contributing to AD often relies on parental report. Pruritus, excoriations, and/or increased eczematous patches hours to days after consumption of a particular food have been reported as signs of food-triggered AD. (11,12) The Expert Panel, from the 2010 NIAID guidelines regarding food allergy, discussed the lack of high-quality

evidence to support elimination diets in the management of AD. Aggressive skin care should be pursued prior to elimination diets. (1) Determining whether a food actually triggers AD requires monitoring and reassessment of the skin four-to-six weeks after diet changes have been implemented. (13)

Negative consequences of prolonged elimination diets include impaired quality of life; nutritional deficiencies; increased financial costs; and loss of tolerance to the avoided food. (2, 13, 14, 15). Oral tolerance has been defined as a state of active non-responsiveness to ingested antigens, resulting from multiple factors, including frequency and forms of exposure. (16; 17) Loss of tolerance has not been extensively studied among children who undergo diet restriction for AD.

In one case series, eleven children developed acute allergic reactions to cow's milk after eliminating it from their diet to help control AD. The AD did not improve, and the children developed reactions ranging from hives to anaphylaxis (18). A fatal reaction to milk following an elimination diet to treat AD has been reported. (19). In another study, nearly 19% of children, with no history of immediate reactions, who pursued an elimination diet to treat AD, based on positive SPT and/or sIgE, developed new, immediate food allergic reactions. Parental reports of reactions that occurred outside a medical setting, and documentation of OFCs, were both used to analyze reactions. Many different food reactions were reported, but 18.3% were to foods than had been consumed prior to elimination without immediate allergic reactions. (2)

The purpose of this study was to examine the frequency of office-based oral food challenge (OFC) failures to foods that had been consumed without immediate reaction, prior to diet elimination to treat AD, based on positive SPT and/or sIgE. Prior studies on this type of loss of tolerance have used self-report and OFCs from multiple settings. This study involved OFCs

done at one pediatric allergy program. This study focused on egg, milk, peanut, soy and wheat, as they are the most common food allergens in the United States.(1) As comparisons for the rate of failure in the AD group, we also assessed the OFC failure rate among children that had OFCs with a history of food allergy, and sensitization only, without any exposure.

METHODS

OFCs performed at the allergy clinics of Riley Hospital for Children at Indiana University Health, in Indianapolis and Carmel, Indiana, from 2008-2014, were analyzed through retrospective chart review. Plain and extensively-heated milk OFCs were grouped together, as were plain and extensively-heated egg OFCs. The institutional IRB considered this study to be IRB-exempt.

Three board-certified allergists conducted all the histories, examinations, laboratory studies and OFCs. Coexisting conditions of allergic rhinitis, asthma, and other food allergy were based on physician diagnosis, most often by clinical history. Regarding asthma, pulmonary function tests were conducted depending on the child's age. Other food allergies were diagnosed using criteria of history, skin testing, and sIgE studies as indicated. SPTs were performed using Greer (Lenoir, NC) extracts, using the Greer pick. The tests were placed on the child's back, and read after fifteen minutes. A positive skin test was defined as having a skin prick test response >3mm bigger than the negative control. Wheal diameter was not measured for the majority of the patients during the timeframe of this review. OFCs were conducted, using the same standardized protocols for each food (9). OFCs were offered if the child had not had an overt clinical reaction to the food in the previous twelve months, and had sIgE levels that suggested a reasonable probability of passing the OFC based on 95% PPVs.(20) OFCs to extensively-heated foods were

offered regardless of sIgE levels. Ten OFCs were offered at higher sIgE levels due to suspected, tolerated exposures. Total IgE levels were not measured on most patients and are not reported. Reasons for food avoidance were classified into three groups: 1) food allergy; 2) sensitization without introduction; and 3) removal from the diet due to positive SPT and/or sIgE results found during AD evaluations. Food allergy was defined as the development of typical signs and symptoms of an allergic reaction—hives, vomiting and respiratory changes—within two hours of ingestion, with supporting SPT or sIgE data. (1, 9) The sensitization group consisted of those who had never been introduced to a food item due to positive SPT and/or sIgE results found during evaluations for AD or other food allergies. Children in the food allergy and sensitization categories had seen both Riley and outside providers for their initial assessments.

Children in the AD group were all known to have consumed the food without any reactions within two hours, but then removed the food from the diet due to SPT and/or sIgE results found during AD evaluations. All of the families that had removed foods for AD purposes had done so based on evaluations by outside providers, prior to visits in the Riley allergy clinics. Reasons for avoidance were documented in the chart during the initial clinic visit and at the time of the OFC. Data were analyzed by SAS v9.4 (SAS Institute, Cary, NC). Analyses and p-values were performed with Wilcoxon non-parametric tests for continuous variables and Fisher's exact test for categorical variables.

RESULTS

A total of 452 OFCs to egg, milk, peanut, soy and wheat were completed from 2008-2014 in the Riley Hospital Allergy Clinics. Ten of the OFCs were excluded from this study as they were missing the reason for food avoidance, leaving 442 OFCs for the final analysis. Table 1 shows the clinical and laboratory background of patients, in relation to the reason for food avoidance.

OFCs were most commonly done because of a history of food allergy (320/442, 72.4%), followed by sensitization (77/442, 17.4%) and then, AD (45/442, 10.2%). There were no significant differences among these three groups regarding age at time of OFC, gender, race, history of asthma and allergic rhinitis, and SPT status. SPTs were done within a year of the OFC in 95.7% of egg OFCs, 94.5% of milk OFCs, 97.8% of peanut OFCs, 78.6% of soy OFCs, and 85.7% of wheat OFCs. The percentage of positive SPTs to the food did not significantly differ among the reasons for food avoidance. Specific IgE studies were done within a year of the OFC on nearly all subjects. The AD group was significantly more likely to have AD ($p<0.0001$), and to have Medicaid insurance ($p=0.004$), versus the food allergy and sensitization groups. The median sIgE at OFC was significantly higher in the AD group, versus the other two groups ($p=0.008$).

Overall, the OFC failure rate was 20.1% (Table 2). There were no significant differences among overall demographics and clinical history between OFC successes and failures. Table 3 shows the reasons for food avoidance in relation to sIgE and SPT results, among individual foods. Median egg IgE was significantly higher in those who had OFCs for egg, with a history of AD. Skin tests were significantly less likely to be positive in those who had OFCs to peanut and milk, with a history of AD. There were no other differences among food allergy, sensitization only, and AD, with regard to median IgE or SPT result. As noted in Table 1, frequency of positive SPTs did not differ among these three groups.

The OFC failure rate for those avoiding a food due to AD was 13.3% (6/45), and did not significantly differ from those avoiding foods due to other reasons (Table ~~3~~4). Of the six OFC failures in the AD group, the reactions involved hives, or hives with one episode of emesis. The failed OFCs involved egg and wheat. All reactions resolved with antihistamines. There was no

significant difference in the length of time of food avoidance in the AD group, between those who passed OFCs (median 26.5 months; range 3-120 months) and those who failed (median 27.0 months; range 3-100 months) (p=0.97). There were also no significant differences among the five foods in OFC outcome, when AD was the initial reason for avoidance (p=0.87).

Figure 1 displays the reasons for food avoidance, in relation to the individual food. Wheat was significantly more likely to be avoided because of AD than the other four foods (p<0.0001). Milk was significantly more likely to have been avoided due to an allergic reaction (p=0.002).

DISCUSSION

In this study, 13.3% of children who had a food removed from their diet due to positive SPT and/or sIgE levels, during an AD evaluation, failed OFCs to that specific food. Tolerance to these foods was lost after the food had been withdrawn from the diet and then not re-introduced until the OFC. Tolerance was lost as early as three months after withdrawal of a food item for this reason.

The rate of OFC failure did not differ significantly in relation to the reason for food avoidance—food allergy, sensitization only, or AD. Data on the role of foods in contributing to AD have been conflicting. Recent evidence suggests a decreasing role for diet in flares of AD. (21) The earliest studies on this topic recommended that close monitoring was necessary to assess the impact of food restriction, and that diet changes alone could not address AD. (22) One recent study that suggested a favorable role for food restriction in AD also emphasized the need for reassessment within three weeks of implementing diet changes to address the skin changes and decide if restriction should continue, and in what manner. (23)

For the general public, food-triggered AD remains a poorly defined entity. Increased itching and changes in skin rashes, with varying timelines, are often attributed to foods. Many of these

changes rely on parent report. Families often have difficulty differentiating causality and coincidence. Changes in skin care are often implemented at the same time as diet changes, creating uncertainties in assessing the impact of food restriction alone. (11, 12) AD is a multi-factorial disease, involving skin inflammation, barrier dysfunction, infection, and other atopic conditions. Adjunctive therapies will need to be used, regardless of any diet changes implemented. (24)

The concept of sensitization to a food, versus actual allergy, continues to create challenges in the implementation of food allergy guidelines. (3) This study adds to the evidence that SPT and sIgE results detected in patients with AD are often clinically irrelevant. (7, 8) Wheat was restricted for AD significantly more than other foods. Wheat avoidance negatively impacts the quality of life of children and families. (25) Many of the OFCs that were performed may have been avoided if patients had timely visits to monitor the significance of their diet changes.

Strengths of this study include the large number of overall OFCs performed. This study is the first to use in-office OFCs to assess loss of tolerance due to dietary avoidance for AD, based on positive SPTs and/or sIgEs. All OFCs were performed at one institution, by three providers, using the same protocol, improving the reliability of the findings. All OFC results are based on clinical observation and documentation, and none rely on parental report. We also focused on the five most common food allergens in the United States. Another study on this issue used parental report and OFCs to assess loss of tolerance. (2)

Limitations include the small numbers of patients who had diet restriction due to AD, versus other causes for food avoidance. We also rely on parental recall as to the initial reasons for avoidance. We lack objective data on the actual value of diet changes on skin issues, with AD

scoring systems such as SCORAD or EASI. Having such data may help identify subsets of children who would benefit from diet changes with their skin condition.

In addition, children with AD often have high serum IgE levels. (26, 27) We did not measure total serum IgE on most of our patients. Knowing these values may have helped place some of the sIgE values in better context. We also used very stringent sIgE criteria in offering OFCs. On one hand, children may have been excluded who could have passed the OFC, altering the overall results. Yet, even with sIgE levels that suggested a reasonable probability of OFC success, 13.3% of children in the AD avoidance group failed their OFCs. Wheal diameters were also not analyzed in this study, and could have potentially provided further information in assessing OFC outcomes among the three groups. However, reviews and studies have suggested that, while there is modest evidence that SPT size may predict which children have a high probability of persistent food allergy, wheal sizes may not predict pass rates for OFCs, or severity of reactions. (20, 28, 29)

Both AD and food allergies are conditions that adversely affect the quality of life and finances of a family. (14, 15) Children with both AD and food allergy also have lower growth compared to their peers who do not have these issues. (30) The consequences of further diet restrictions on growth will need further study. Loss of tolerance to a food once consumed without immediate reactivity must now be considered another risk of removing foods based on testing results in the context of AD, particularly without appropriate follow up. If such diet changes are implemented, families may also need education on anaphylaxis and use of epinephrine. There was a wide range in length of food avoidance before OFCs, but one case of tolerance was lost after only three months of restriction.

In conclusion, 13.3% of children who had foods consumed without any immediate reaction, but then removed from the diet to address AD, based on SPT and sIgE results, failed OFCs, losing tolerance to that food. The OFC failure rate for AD did not differ from the OFC failure rates for food allergy and sensitization. Eliminating these commonly-consumed foods significantly affects the quality of life for the child and the family. Primary care providers need to counsel families on the limits of allergy testing and diet changes in addressing AD. Families should be advised to consistently use measures of skin hydration, emollients, and topical medications to address AD. Any diet changes that are pursued to manage AD must be done so with extreme caution. The risks of IgE-mediated allergic reactions on food reintroduction may outweigh the value of food elimination on AD management. Families and providers need to be aware of the risks of excessive testing and diet manipulation in trying to manage AD, including loss of tolerance.

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None

CONFLICT OF INTEREST

Dr Leickly, Dr Kloepfer, and Dr Vitalpur have been investigators on the PALISADES study from Aimmune.

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Figure 1. Frequencies of Reasons for Food Avoidance (in percentage) in Relation to Individual Foods: Wheat was significantly more likely to be avoided due to AD (p<0.0001). Milk was significantly more likely to be avoided due to food allergy (p=0.0002).

Table 1. Clinical and Laboratory Background of Patients in relation to reason for Food Avoidance.

	Overall (n=442)	Food Allergy (n=320; 72.4%)	Sensitization Only (n=77; 17.4%)	Atopic Dermatitis (n=45; 10.2%)	p-value
Age at OFC (median years)	5 (0.9 – 16)	5 (0.9 – 16)	5 (1 – 15)	4 (1 – 14)	.39
Female (n; %)	144 (32.6)	106 (33.1)	28 (36.4)	10 (22.2)	.25
Race (n; %)					
White	257 (81.7)	257 (81.6)	67 (87.0)	33 (73.3)	.36
Black	40 (9.2)	29 (9.2)	4 (5.2)	7 (15.6)	
Other (Asian; biracial)	40 (9.2)	29 (9.2)	6 (7.8)	5 (11.1)	
Medicaid (n; %)	73 (16.5)	57 (17.8)	4 (5.2)	12 (26.7)	.004*
Asthma (n; %)	164 (37.1)	119 (37.2)	27 (35.1)	18 (40.0)	.86
Atopic Dermatitis (n; %)	230 (52.0)	141 (44.1)	48 (62.3)	45 (100.0)	<.0001*
Allergic Rhinitis (n; %)	113 (25.6)	80 (25.1)	20 (26.0)	13 (28.9)	.86
Other food allergy (n; %)	204 (46.2)	126 (39.4)	53 (68.8)	25 (55.6)	<.0001*
Spt + (n; %)	197 (44.6)	135 (42.2)	40 (52.0)	22 (48.9)	.25

Values are medians (ranges) for continuous variables and frequencies (percentages) for categorical variables. P-values are from Wilcoxon rank-sum tests and Chi-Square tests, respectively.

Table 2. Demographics of Patients having OFCs.

	Overall (n=442)	Failed OFCs (n=89; 20.1%)	Passed OFCs (n=353; 79.9%)	p-value
Age (median years)	5 (0.9 – 16)	5 (1 – 14)	5 (0.9 – 16)	.14
Female	144 (32.6)	29 (32.6)	115 (32.6)	.99
Race				
White	257 (81.7)	75 (87.2)	282 (80.3)	.12
Black	40 (9.2)	8 (9.3)	32 (9.1)	
Other	40 (9.2)	3 (3.5)	37 (10.5)	
Medicaid	73 (16.5)	9 (10.1)	64 (18.1)	.07
Asthma	164 (37.1)	36 (40.5)	128 (36.3)	.46
Atopic Dermatitis	230 (52.0)	40 (44.9)	190 (53.8)	.13
Allergic Rhinitis	113 (25.6)	22 (24.7)	91 (25.9)	.83
Other Food Allergy	204 (46.2)	35 (39.3)	169 (47.9)	.15

Values are medians (ranges) for age and frequencies (percentage) for the categorical variables. P-values are from Wilcoxon rank-sum tests and Chi-Square tests, respectively. There were no significant differences between those who passed, and those who failed, OFCs.

Table 3. Reasons for food avoidance in relation to specific IgE levels among individual foods (n=443).

	Food allergy (n=320)	Sensitization only (n=77)	Atopic Dermatitis (n=45)	p-value
Egg	0.38 (0 – 57.5)	0.41 (0 – 90.8)	0.64 (0 – 49.9)	.03
Milk	0.38 (0 – 93.1)	0.58 (0.58 – 0.58)	0 (0 – 10.6)	.54
Peanut	0 (0 – 7.9)	0 (0 – 16.3)	0 (0 – 0)	.26
Soy	1.01 (0 – 13.6)	2.6 (1.9 – 3.4)	13.3 (2.1 – 21.4)	.14
Wheat	2.18 (0 – 39.9)	1.9 (1.9 – 1.9)	1.11 (0 – 67)	.93

Values are medians, in ku/l, (ranges) for specific IgE values. P-values are from Wilcoxon rank-sum tests and Chi-Square tests, respectively. Median egg IgE was significantly higher in those who had OFCs for egg, with a history of AD.

Table 4. Reason for Food Avoidance in relation to OFC Outcome (N=442).

	OFC Pass (N=353; 79.9%)	OFC Fail (N=89; 20.1%)
Food Allergic Reaction (n=320; 72.4%)	250 (78.1%)	70 (21.9%)
Sensitization only (never ingested) (n=77; 17.4%)	64 (83.1%)	13 (16.9%)
AD (n=45; 10.2%)	39 (86.7%)	6 (13.3%)

Reaction history was not associated with OFC outcome (p=0.30).

Table 5. OFC outcome for Foods avoided as Suspected AD Triggers.

Foods (n=45)	Fail (n=6; 13.3%)	Pass (n=39; 86.7%)
Egg (n=24) (Plain & extensively heated)	4 (16.7)	20 (83.3)
Milk (n=9) (Plain & extensively heated)	0 (0)	9 (100)
Wheat (n=6)	2 (33.3)	4 (66.7)
Soy (n=3)	0 (0%)	3 (100)
Peanut (n=3)	0 (0%)	3 (100)

There was no significant difference among the five foods with regard to OFC pass-fail rates, when the initial reason was suspected AD trigger. (p=0.33; NS)

Figure 1.